Cyst Fluid Analysis in the Differential Diagnosis of Pancreatic Cysts

A Comparison of Pseudocysts, Serous Cystadenomas, Mucinous Cystic Neoplasms, and Mucinous Cystadenocarcinoma

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Pancreatic cystic lesions include inflammatory pseudocysts, benign serous tumors, and mucinous neoplasms, some of which are malignant. Clinical and radiologic indices are often inadequate to discriminate reliably among these possibilities. In an attempt to develop new preoperative diagnostic criteria to assist in decisions regarding therapy, the authors have performed cyst fluid analysis for tumor markers (carcinoembryonic antigen: CEA, CA 125, and CA 19.9), amylase content, amylase isoenzymes, relative viscosity, and cytology on 26 pancreatic cysts. The cases included nine pseudocysts, five serous cystadenomas, 4 mucinous cystic neoplasms, 7 mucinous cystadenocarcinomas, and one mucinous ductal adenocarcinoma with cystic degeneration. Carcinoembryonic antigen levels were high (>367) in all benign and malignant mucinous cysts, but were low (<23) in the pseudocysts and benign serous cystadenomas, an indication that CEA discriminates between mucinous and nonmucinous cysts ($p < 0.0001$). Values for CA 125 were high in all malignant cysts, low in pseudocysts, and variable in mucinous cystic neoplasms and serous cystadenomas. Levels of Ca 19.9 were nondiscriminatory. Cyst fluid amylase and lipase content were variable but were generally high in pseudocysts and low in cystic tumors. Amylase isoenzyme analysis was useful to differentiate pseudocysts from cystic tumors. Measurement of the relative viscosity in cyst fluid showed high (> serum viscosity) values in 89% of mucinous tumors and low values (< serum) in all pseudocysts and serous cystadenomas ($p < 0.01$). Cytologic analysis of cyst fluids was of limited value in differentiating pseudocysts from serous cystadenoma, but in seven of eight mucinous tumors provided useful diagnostic information and correctly classified three of five malignant tumors. The authors conclude that cyst fluid analysis can provide a preoperative classification of these diagnostically difficult lesions. The combination of viscosity, CEA, CA 125, and cytology can reliably distinguish malignant cystic tumors and potentially premalignant mucinous cystic neoplasms from pseudocysts and serous cystadenomas. Amylase content with isoenzyme analysis is useful to identify pseudocysts.

Most pancreatic cystic lesions are inflammatory pseudocysts. A small percentage (about 10%) of pancreatic cysts are neoplastic ductal lesions such as benign serous (microcystic or glycogen-rich) cystadenomas, and mucinous tumors, designated as mucinous cystic neoplasms and mucinous cystadenocarcinomas.[1-3] Rare entities that may result in pancreatic cysts include papillary cystic tumors, cystic islet cell tumors, lymphoepithelial cysts, and ductal adenocarcinomas with cystic degenera-

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tion. Distinguishing pseudocysts from cystic tumors is essential to planning appropriate surgical management.[2] The need to differentiate between serous and mucinous tumors before operation is less clear because both types of tumors are usually resected. Some authors favor observation of asymptomatic serous cystadenomas,[3–5] but this recommendation is of limited practical value because the tumor type is often not known before resection.

There are no reliable clinical or radiologic criteria to permit preoperative differentiation of the different types of pancreatic cysts.[2] The finding of multilocularity on computed tomographic scan is helpful because many neoplasms are multilocular, whereas pseudocysts are almost always unilocular. Cystic tumors (either serous or mucinous), however, also may be unilocular.[2] The microcystic subgroup of serous cystadenoma may exhibit a characteristic central scar with "starburst" calcifications, but these features are present in only a minority of cases.[2] In a review of cystic tumors referred to our institution, fully one third of the cases had been diagnosed previously as pseudocysts[2] and many were inappropriately treated as a result.[6] In particular, 40% of mucinous tumors were misdiagnosed as pseudocysts.[2]

Intraoperative differentiation of pancreatic cysts by frozen section histopathologic analysis of biopsy material may permit a definitive diagnosis, but this procedure is notoriously unreliable.[2,6] Several factors complicate the diagnosis of pancreatic cysts on biopsy specimens.[2] First, cystic tumors may exhibit extensive denudation of the cyst lining epithelium and therefore masquerade as pseudocysts. For this same reason, a definitive diagnosis of pseudocyst can never be made on biopsy material. Second, the epithelium of mucinous tumors usually contains an admixture of serous (up to 95%) and mucinous components, which may lead to misclassification of a tumor on frozen section or biopsy specimens. Finally, in mucinous cystadenocarcinomas, the malignant portion of the cyst lining may represent only a small focus in an otherwise benign-appearing tumor, further complicating the correct classification of the neoplasm.

Cyst fluid analysis of pancreatic cysts for chemical analysis (amylase content), tumor markers (carcinoembryonic antigen [CEA], CA 19.9), and cytology has been described.[2,6–11] Unfortunately, the number of cases in these studies is too small to accurately assess the value of this procedure in the differential diagnosis of pancreatic cysts. The relative rarity of cystic pancreatic neoplasms makes the accumulation of large series extremely difficult.

We have analyzed the cyst fluid in 26 cases of pancreatic cysts including 9 pseudocysts, 5 serous cystadenomas, 4 mucinous cystic neoplasms, 7 mucinous cystadenocarcinomas, and 1 mucinous ductal carcinoma with cystic degeneration. The analysis included cytology, cyst fluid viscosity, CEA, CA 19.9, CA 125, amylase and lipase content and amylase isoenzyme analysis. The improved differential diagnosis provided by these data suggests additional criteria to guide the management of patients with pancreatic cystic lesions.

MATERIALS AND METHODS

Cyst fluid was obtained from pancreatic cysts in 26 patients (7 men, 19 women) undergoing surgical exploration for pancreatic cystic lesions. The cyst fluid was collected by intraoperative needle aspiration or, when complete resection was planned, by needle aspiration immediately after surgical removal of the cyst. The diagnosis in all cases was confirmed by histopathologic examination of the resected specimen, or, in the case of pseudocysts and unresectable tumors, by examination of biopsy material. In one additional case (a "microcystic" serous cystadenoma), no fluid could be aspirated. The fluid was immediately clarified by centrifugation and smears prepared from the pellet material for cytologic analysis. Smears were fixed in 95% ethanol and stained either with hematoxylin and eosin or by the Papanicolaou technique. Interpretation of the smears was performed by a single surgical pathologist who was blinded to the identity of the cyst. The clarified fluid was aliquoted and frozen at −70 C for future analysis.

The cyst fluid relative viscosity (RV) was measured on an Ostwald viscometer at 37 C using distilled water (RV = 1.0) as a standard (serum RV reference range, 1.40 to 1.80). Cyst fluid chemistry analysis was performed on an Hitachi 717 autoanalyzer and included amylase, alkaline phosphatase (ALP), 5'-nucleotidase (5'-N), and total protein. Lipase levels were measured on a Dupont ACA IV analyzer. Amylase isoenzyme analysis was performed by polyacrylamide gel electrophoresis.[12] The tumor markers CEA, CA 125, and CA 19.9 were measured using commercial solid-phase double-antibody sandwich immunoassays (CEA: Abbott Laboratories, CEA-EIA kit, No 83-4745/R2, serum reference range < 3.0 ng/mL; CA 125: Abbott Laboratories, Ca 125-EIA, No 7007, serum reference range < 20 U/mL; CA 19.9: CIS International, serum reference range < 37 U/mL).

RESULTS

The volume of fluid collected from the cystic lesions varied from 3 to 150 mL. The color, turbidity, and presence of cellular/tissue debris were variable and did not allow discrimination among any of the categories of cysts.

Viscosity

The cyst fluids were mucoid and viscous on gross inspection in 10 of 11 mucinous tumors, whereas the fluid from pseudocysts and serous cystadenomas was always thin and watery. A quantitative assessment of viscosity was performed by measurement of cyst fluid relative viscosity. These values are shown in Table 1. With water as a standard (RV = 1.0) and serum (RV = 1.4–1.8) for comparison, all of the pseudocysts (n = 9) and serous cystadenomas (n = 5) had low RV values with mean values less than serum (pseudocysts mean = 1.24, standard deviation [SD] = 0.12, serous cystadenoma mean = 1.25, SD = 0.16). In contrast, the RV values in eight of nine (89%) of the mucinous tumors and in the single case of mucinous ductal carcinoma with cystic degeneration were higher than serum. The difference between the nonmucinous cysts (serous cystadenoma and pseudocysts) and mucinous cysts (mucinous cystic neoplasms and mucinous cystadenocarcinomas) is statistically significant ($p < 0.0001$) using the one-sided Fisher's exact test. In four cases the fluid was too viscous to flow through the viscometer. These four cases were assigned relative viscosity values equal to the highest measured viscosity for the purpose of statistical calculations (assigned value = 30). The one mucinous cystic tumor with a low relative viscosity exhibited extensive denudation of the cyst lining epithelium in histopathologic sections, and the remaining nonsloughed epithelium was predominantly (~95%) serous. The relative viscosities of the benign pseudocysts and serous cystadenomas combined yield a mean of 1.24, SD = 0.13. All of the benign cysts had relative viscosities less than a cutoff value of 1.63 defined as the mean plus 3 standard deviations. In contrast, nine of ten mucinous and malignant tumors had relative viscosities above this cutoff value.

Table 1. BIOCHEMICAL PARAMETERS OF PANCREATIC CYST FLUIDS

Diagnosis Viscosity	CEA (ng/mL)	CA 125 (U/mL)	CA 19.9 (U/mL)	Amylase (U/L)	Lipase (U/dL)
Pseudocyst					
1.18	<2.0	1.9	—	34,080	1810
1.14	—	6.0	—	—	—
1.16	9.3	47.3	>24,000	11,830	1240
1.24	—	7.0	—	—	—
1.47	22.9	26.2	3400	1070	6510
1.42	11.3	14.1	15,400	36,610	580
1.17	2.3	29.8	420	543	62
1.22	2.2	22.0	—	6810	710
1.15	2.5	7.9	—	982	100
SCA					
1.20	<0.5	1153	—	44	17
1.43	2.5	53	450	790	200
1.05	0.0	543	12	153	36
1.42	1.8	90	29	630	12
1.16	<0.5	2.0	—	830	114
MCN					
>30	696	9.7	—	34,410	—
1.20	367	25	—	288,830	4290
>30	9330	111	—	38	13
—	18757	798	—	47	21
MCAC					
1.84	5050	395	—	60	21
3.00	688	210	—	58	—
—	15250	2130	—	33	55
>30	3200	210	—	1530	42
>30	57,020	2649	—	—	42
2.92	42,730	16,429	>24,000	570	155
3.80	31,720	3066	58	42	7
CCD					
1.89	4580	55,422	800	284	—

Viscosity, time of sample/time of water; SCA, serous cystadenoma; MCN, mucinous cystic neoplasm; MCAC, mucinous cystadenocarcinoma; CCD, mucinous ductal carcinoma with cystic degeneration.

Tumor Markers

Values for cyst fluid CEA, CA 125, CA 19.9, amylase, and lipase are shown in Table 1. The CEA levels in both pseudocysts (mean, 7.5 ng/mL, SD = 7.5) and serous cystadenomas (mean 1.1 ng/mL, SD = 1.0) were low and did not overlap with those of the mucinous cystic neoplasms (mean, 7288 ng/mL; range, 367 to 18,757) or mucinous cystadenocarcinomas (mean, 22,239 ng/mL; range, 688 to 57,020). The difference between the mucinous and nonmucinous groups was highly significant ($p < 0.0001$, one-sided Fisher's exact test). Values for the pseudocysts overlapped with those of the serous cystadenomas, and values for the mucinous cystic neoplasms overlapped with those of the mucinous cystadenocarcinomas. The CEA level was also high in the one case of adenocarcinoma with cystic degeneration. An upper cutoff value for cyst fluid CEA (mean +3 SD of the combined pseudocyst and serous cystadenoma groups) of 24.7 ng/mL yielded a sensitivity and specificity of 100% in predicting a mucinous or malignant pancreatic tumor. Values below 24.7 ng/mL were both 100% sensitive and specific for benign serous cystadenomas and pseudocysts. Very high CEA values suggest malignancy.

The CA 125 levels were low in all pseudocysts (mean, 18.0 U/mL; SD = 13.5) and significantly higher in all malignant cysts (mean, 10,064 U/mL; range, 210 to 55,422). The values in the serous cystadenomas and mucinous cystic neoplasms overlapped with those of pseudocysts and with the lower range of the values for malignant cysts.

CA 19.9 was measured in 10 of our 25 cases. The CA 19.9 levels were quite variable and high values were observed in pseudocysts, microcystic adenomas, and mucinous cystadenocarcinomas.

Enzymes

The amylase level was high in seven of seven pseudocysts (mean, 13,132) but was variable in cystic tumors (range, 33 to 288,830). Lipase values also were high in most pseudocysts (mean, 1573 U/dL) and were low in most of the cystic tumors. Neither amylase or lipase reliably discriminated between the different types of cysts, but low values suggested a cystic tumor. An analysis of amylase isoenzymes was performed on five pseudocysts and 15 of the cystic tumors. Electrophoretograms were interpreted by one of the authors (ALW), who was blinded to the identity of the specimens. The cystic tumors exhibited various combinations of the normal P1 (pancreatic) and S1 (salivary) isoenzymes and an unidentified slow migrating peak. However, in four of five of the pseudocysts the P2 peak was prominent as well as the P1 (a pattern typical of the "old amylase" found in pseudocysts[12,13]). In one pseudocyst, the peaks exhibited an ambiguous pattern and could not be definitively characterized.

The levels of ALP (<10 to 94 U/L), 5'N (3 to 340 U/L), and total protein (3.0 to 52.0 g/L) in the different cyst types were generally low and nondiscriminatory (data not shown).

Cytology

The results of the cyst fluid cytologic analysis are shown in Table 2. Of the eight mucinous tumors on which cytologic analysis was performed, mucin-containing epithelium was identified in seven (87.5%). Among the malignant tumors (five cases), three (60%) exhibited malignant cells, one contained atypical epithelium suspicious for malignancy, and one was nondiagnostic. Cytologic smears on two of three serous cystadenomas were misclassified as inflammatory cysts by virtue of the absence of epithelium and the presence of polymorphonuclear leukocytes, histiocytes, and tissue debris. In one case, clusters of simple nonmucinous epithelium were observed and the tumor was correctly classified. All five

Table 2. CYTOLOGIC ANALYSIS OF PANCREATIC CYST FLUIDS

Diagnosis	Cytologic Interpretation
Pseudocyst	5/5: Inflammatory, no evidence of malignancy
SCA	2/3: Inflammatory, no evidence of malignancy
	1/3: Clusters of simple nonmucinous epithelium consistent with SCA
MCN	4/4: Mucinous epithelial cells present
MCAC	2/4: Malignant mucinous epithelial cells present
	1/4: Atypical mucinous epithelial cells present
	1/4: Nondiagnostic
CCD	1/1: Malignant mucinous epithelial cells present

SCA, serous cystadenoma; MCN, mucinous cystic neoplasm; MCAC, mucinous cystadenocarcinoma; CCD, mucinous ductal carcinoma with cystic degeneration.

pseudocysts were correctly classified as inflammatory lesions.

In addition to the cases described in Tables 1 and 2, we have also encountered one case of a mucinous cystic neoplasm that was unusual in that the tumor communicated directly with the pancreatic duct. This anatomic arrangement, in our experience, is uncommon, and would permit drainage of the tumor contents and mixing with normal pancreatic secretions, thus potentially altering the cyst fluid values. Fluid from this case had a relative viscosity of 1.83, a CEA of 23 ng/mL, a CA 125 of 13 U/mL, an amylase of 9553 U/L, and a lipase of 20, and the cytologic smears showed rare atypical and degenerated epithelial cells indicative of a cystic tumor.

DISCUSSION

Distinguishing pseudocysts from cystic neoplasms is difficult by clinical and radiologic criteria.[2] Differentiating benign serous from mucinous (mucinous cystic neoplasms) and malignant mucinous neoplasms (mucinous cystadenocarcinomas) is equally problematic. In an earlier study, we reported that fully one third of cystic neoplasms referred to our institution were previously misdiagnosed as pseudocysts, and many were inappropriately treated as a result.[2,6] Intraoperative biopsy of pancreatic cysts for frozen section histopathologic diagnosis is useful but, in our experience, fails to correctly classify a pancreatic cystic neoplasm in 20% of cases. This is because some tumors show extensive epithelial denudation of the cyst lining epithelium (thus masquerading as pseudocysts) and because the mucinous or malignant component of the epithelium may be only focal (resulting in misclassification of the tumor).[2]

Although there is general agreement that mucinous tumors should be resected, some authors[3-5] favor observation of asymptomatic serous cystadenomas. Asymptomatic pseudocysts are often treated expectantly; *in situ* drainage is usually favored for those that come to therapy. Better preoperative and intraoperative tests are needed to distinguish between the different types of pancreatic cysts before the requisite therapeutic decisions.

Pancreatic cyst fluid can be obtained before operation by ultrasound or computed tomography-guided percutaneous needle aspiration or during operation. Tests performed on samples collected during operation must be both rapid to perform and immediately available. Cyst fluid viscosity, cytology, and enzyme analysis can meet this requirement. The tumor markers CEA and CA 125 require longer processing times that exceed intraoperative limits. Therefore, measurement of tumor markers is only practical as a preoperative procedure on percutaneous needle aspirates.

The cumulative experience with percutaneous cyst fluid analysis reported in the literature is limited. Yu and

Shetty[8] described one case of a mucinous cystadenocarcinoma with a high (6000 ng/mL) CEA content, and Tatsuta et al.[9] reported high CEA levels in five cases of mucinous cystadenocarcinoma (mean = 17,782 ng/mL), low values in eight pseudocysts (mean, 3.0 ng/mL), and intermediate low values in three cases of what they designated as "cystadenomas" (mean, 15 ng/mL). These differences were significant ($p < 0.001$). It is not clear, however, how the diagnoses were confirmed. Furthermore, the authors use of the generic term "cystadenoma" is confusing because this could represent either a serous cystadenoma or a mucinous cystic neoplasm. Pinto and Meriano[11] reported high mean CEA levels in mucinous cysts (2214.1 ng/mL) and cystic pancreatic adenocarcinomas (3379.9 ng/mL) and low mean levels in pseudocysts (3.2 ng/mL). They determined that a cutoff value of 5 ng/mL would discriminate between mucinous lesions and adenocarcinomas with 100% sensitivity and 64% specificity. Two serous cystadenomas exhibited low values. Unfortunately, it is unclear from their data whether mucinous cystadenocarcinomas were included in the mucinous tumor group or in the adenocarcinoma group.

Our data confirm these earlier reports that cyst fluid CEA levels are useful for differentiating among pancreatic cysts. Based on the cumulative experience, it appears that CEA is primarily useful for differentiating mucinous and malignant tumors (mucinous cystic neoplasms, mucinous cystadenocarcinomas, and cystic ductal adenocarcinomas) from nonmucinous cysts (pseudocysts and serous cystadenomas). High cyst fluid CEA levels do not predict malignancy, but rather indicate that the cyst is either malignant or of the mucinous type. From a practical point of view, all mucinous cystic neoplasms are considered premalignant and do not require a preoperative distinction from mucinous cystadenocarcinomas because both should be resected. An upper cutoff value for cyst fluid CEA of 26 ng/mL using the Abbott EIA assay kit appears to allow reliable discrimination between benign lesions and mucinous or malignant cysts. The only exception to this that we have encountered was the one unusual case of a mucinous tumor that communicated with the pancreatic duct (CEA = 23 ng/mL). The high fluid relative viscosity and the finding of atypical epithelial cells in this case would indicate a neoplastic (mucinous) cyst. The low CEA value probably resulted from drainage of the tumor contents into the pancreatic duct. This case illustrates the potential pitfalls that may be encountered when unusual cysts are examined. Caution is therefore advised when interpreting isolated values. The CEA cutoff value used by Pinto and Meriano[11] (5 ng/mL, also Abbott EIA kit) may be too low, because three of our pseudocysts were above this level.

CA 125 has not been measured previously in pancreatic cysts. All mucinous cystadenocarcinomas showed significantly higher CA 125 levels than did pseudocysts. Serous cystadenomas exhibited variable values, as did the four cases of mucinous cystic neoplasm. The CA 125 levels of serous cystadenomas overlapped with those of malignant cysts on the high side and with mucinous cystic neoplasms and pseudocysts on the low side. Thus, very high CA 125 levels appear to be predictive of malignancy and low values of a benign tumor. The combination of CA 125 with a high CEA level may help to distinguish mucinous cystic neoplasms (lower CA 125) from mucinous cystadenocarcinomas (high CA 125). The number of mucinous cystic neoplasms in our study, however, is currently too small to confirm this possibility. More experience with CA 125 levels in pancreatic cysts is required to confirm the usefulness of this tumor marker.

We have measured cyst fluid CA 19.9 in a limited number of pancreatic cysts. The levels were highly variable and nondiscriminatory. Our results conflict with the findings of one previous study[10] in which CA 19.9 was measured in four pancreatic cystic tumors. These included two carcinomas with high levels (100,000 and 320,000 U/mL) and two so-called "cystadenomas" with low values (14 and 20 U/mL). In our series, the CA 19.9 level in one serous cystadenoma was 420 (eight times higher than the value of 58 obtained from a mucinous cystadenocarcinoma), and both pseudocysts and mucinous cystadenocarcinomas yielded values of >24,000. The fact that pseudocysts may show high CA 19.9 values should not be surprising because this marker also may be elevated in the serum of patients with pancreatitis.[14]

Cyst fluid relative viscosity appears useful for distinguishing most mucinous tumors (benign and malignant) from nonmucinous cystic tumors and pseudocysts cysts (89% sensitivity, 100% specificity) when an upper cutoff value of 1.63 is used. Values below this cutoff strongly suggest, but do not prove, that a cyst is benign. In many cases, the increased viscosity is apparent grossly, but quantitative viscometry may be performed rapidly. Viscosity determination has never before been reported on pancreatic cyst fluids. We believe that this test shows promise for both preoperative and intraoperative differentiation of mucinous neoplasms from nonmucinous cysts.

A number of authors have reported measuring the amylase content of pancreatic cysts.[2,7,11] The amylase content of pseudocysts is almost always high, whereas the level in neoplastic cysts has generally been thought to be low,[2] although there are two case reports to the contrary.[15,16] Recently, Pinto and Meriano[11] reported variable cyst fluid amylase levels in a variety of pancreatic cysts and concluded that this test performed poorly in discriminating different cyst types. Our current results confirm the finding of elevated amylase levels in pseudocysts, but we also have found that cystic tumors of all types may exhibit high cyst fluid amylase levels. Analysis of amylase isoenzymes in pancreatic cysts appears to have value in distinguishing pseudocysts (prominent P1 and P2 isoenzymes) from cystic tumors (variable mixtures of P1, S1, and a slow migrating unidentified peak) but does not differentiate the different tumor types. More experience with cyst fluid isoenzyme analysis is necessary to determine the value of this procedure.

Cyst fluid lipase measurements have not been previously reported. High levels were observed in most pseudocysts, whereas cystic tumors generally exhibited lower levels. Like amylase content, lipase values are unreliable in individual cases but may be useful when interpreted in conjunction with other cyst fluid parameters. The fact that some tumors exhibit a high amylase or lipase content is not unexpected because these tumors may have extensive epithelial denudation. This process would transform these tumors into structures that resemble a pseudocyst.

Cytologic analysis of pancreatic cyst fluid aspirates has been previously reported on a limited number of cases.[2,9-11,17] We previously reported four cases of cystic tumors in which cytologic preparations showed mucinous epithelial cells and two showed evidence of malignancy.[2] Jones et al.[17] reported three mucinous cystic tumors containing mucus-secreting columnar cells with abundant background mucin and one serous cystadenoma with sheets of cuboidal cells typical of a serous neoplasm. Tatsuta et al.[9] reported a correct cytologic diagnosis on four of six (66%) malignant cysts, but gave no data on pseudocysts, serous cystadenoma, or mucinous cystic neoplasms other than to state that "no cancer cells" were observed. Pinto and Meriano[11] reported finding mucinous epithelial cells in two of five mucinous cystic tumors and malignant cells in six of 11 adenocarcinomas and concluded that cyst fluid cytologic examination was an insensitive diagnostic approach. Our results show that cytology is useful to differentiate mucinous from nonmucinous cysts, may provide definitive evidence of malignancy, but cannot reliably distinguish pseudocysts from serous cystadenoma. A positive diagnosis of inflammatory pseudocyst cannot be made definitively by cytologic analysis alone because abundant inflammatory cells and histiocytes in the absence of demonstrable epithelium may be observed in any degenerated cystic tumor. False negatives for tumor are a practical problem because some neoplastic cyst fluids contain no tumor cells. In the case of malignant tumors, the epithelial cells may appear benign, especially in tumors where the malignant component is focal. Therefore, cytology is only helpful if positive, and caution in interpretation is advised to avoid misclassification of the cyst. The principal advantage of cytology (like biopsy) is that a definitive diagnosis is possible in a significant percentage of malignant tumors.

Our results demonstrate that analysis of cyst fluid with a panel of diagnostic parameters is an accurate means to differentiate among various types of pancreatic cysts. In addition to evaluating CEA and cytology, we also have reported four new parameters (relative viscosity, CA 125, amylase isoenzyme analysis, and lipase) that appear useful. The combination of CEA, CA 125, cyst fluid RV, amylase isoenzymes, and cytology correctly classifies most cysts, identifies malignancy, and differentiates mucinous from nonmucinous cysts (serous neoplasms and pseudocysts). Amylase and lipase content are helpful but not definitive. Table 3 summarizes the expected cyst fluid parameters in different types of pancreatic cysts. Cumulatively these tests are more sensitive and specific than radiologic criteria or the histopathologic analysis of biopsy material and can be performed before operation on cyst fluid aspirates.

Percutaneous aspiration of pancreatic cysts has been reported.[7,9,11] Resistance to implementing this technique mainly centers on the possibility that malignant cells could be seeded either into the peritoneum or along the needle tract,[2] as has been documented in ductal adenocarcinoma of the pancreas. The potential risk of seeding cystadenocarcinoma is unknown, but in our opinion, is probably exceeded by the consequences of misdiagnosis with resultant inappropriate treatment.

Our study does not include the rare forms of pancreatic cystic neoplasms (*e.g.*, lymphoepithelial cysts, solid and cystic tumors, and the occasional cystic islet cell tumor) and therefore cannot be applied to them. These comprise fewer than 8% of cystic neoplasms, however, and less than 1% of all pancreatic cystic lesions. Our one

Table 3. CYST FLUID INDICES USEFUL IN DIFFERENTIAL DIAGNOSIS

Diagnosis	Viscosity	CEA	CA 125	Enzymes	Cytologic Findings
PSEUDOCYST	Low	Low	Low	High (isoamylase diagnostic)	Negative
SCA	Low	Low	Variable	Variable	Negative
MCN	Usually high	High	Variable	Variable	Usually positive
MCAC	High	High	High	Variable	Usually positive

SCA, serous cystadenoma; MCN, mucinous cystic neoplasm; MCAC, mucinous cystadenocarcinoma.

case of a malignant adenocarcinoma with cystic degeneration was correctly identified as a malignancy by cyst fluid analysis.

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